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Translational Regulation of PDGF2/c-sis Proto-Oncogen during Megakaryocytic Differentiation

Platelet-derived growth factor (PDGF) is a homo- or hetero-dimer of A and B chains that serves as a potent mitogen of all cells of mesenchymal origin. The B chain (PDGF2) is the c-sis proto-oncogen known to be involved in cellular transformation. PDGF has a major role in wound healing as well as in embryogenesis and development. Overexpression of this mitogen has been found in many types of human tumor cells, and is also linked to chromic myeloproliferative disorder which is developed to terminal acute leukemia in 15% of the patients. The current hypothesis for the pathogenesis of myelofibrosis involves the intramedullary release of growth factors such as PDGF from megakaryocytes and/or platelets. Additional information about the mechanisms controlling the level of PDGF synthesis during megakaryopoesis might shed light on the process leading to malignancy. Coinciding with other oncogens encoding regulatory proteins, PDGF2 expression in highly regulated at multiple levels. Information has been accumulated about regulatory elements controlling the synthesis of PDGF2 mRNA and its stability. However, mechanisms controlling the rate PDGF2 protein synthesis are not fully understood yet. Recently we have been able to demonstrate that during megakaryocytic differentiation the syntheses level of a protein encoded by mRNA harboring PDGF2 regulatory sequences is temporarily magnified. Our data suggest that there are cell-type specific transient changes in the transnlational machinery which differentially lead to efficient PDGF2 translation during megakaryocytic differentiation. The broad goal of the proposed research is to study this regulatory mechanism by further characterization of the involved cis- and trans-acting factors.

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Molecular Analysis of MLL/11q23 Secondary Acute Leukemias

It is well documented that chemotherapy for cancers can have serious side effects. One of the most serious of those side effects is the induction of a new leukemia independent of the cancer originally treated with the chemotherapy. Unfortunately a very useful class of anti-cancer drugs, the "topoisomerase II inhibitors," in 5% of patients treated for various malignancies cause a fatal leukemia within a few years of their use. This leukemia characteristically has translocations involving the 11q23 cytogenetic locus. At a molecular level these translocations occur in the MLL gene activating it to become an oncogene. It is thought that because topoisomerase II inhibitors have been shown to cause DNA breaks *in vitro* that they are fundamental to the mechanism which generates the translocations involving MLL. It is the goal of this work to determine if topoisomerase II inhibition does lead to MLL/11q23 translocations and if so to understand how at molecular level the translocations occur. If the translocation mechanism is better understood, better topoisomerase II inhibitors or ways of administering them without the leukemogenic side effects could be developed.